Perspectives in PSYCHIATRIC CARE

Perspectives in Psychiatric Care ISSN 0031-5990

Column

Biological Perspectives

Are Neuroleptic Malignant Syndrome and Serotonin Syndrome the Same Syndrome?

Debbie Steele, PhD, RN, Norman L. Keltner, EdD, RN, and Teena M. McGuiness, PhD, CRNP, FAAN

Debbie Steele, PhD, RN, is an Assistant Professor, Department of Nursing, California State University, Fresno, California, USA; Norman L. Keltner, EdD, RN, is a Professor, School of Nursing, University of Alabama, Birmingham, Alabama, USA; and Teena M. McGuiness, PhD, CRNP, FAAN, is a Professor, School of Nursing, University of Alabama, Birmingham, Alabama, USA.

Search terms:
Neuroleptic malignant syndrome, serotonin syndrome

Author contact: nkeltner@uab.edu, with a copy to the Editor: gpearson@uchc.edu
doi: 10.1111/j.1744-6163.2010.00292.x

The title question is interesting to contemplate. The basic elements of these two syndromes are similar, and some researchers believe them to ". . . exist on a spectrum of the same disorder" (Demirkiran, Jankovic, & Dean, 1986; Fink, 1996; Nisijima, Shioda, & Iwamura, 2007). Obviously, neuroleptic malignant syndrome (NMS) is caused by antipsychotic and other dopamine-compromising drugs, while serotonin syndrome (SS) is caused primarily by antidepressant and other serotonin-enhancing agents. Since the causative factor is dopamine hypofunction in the first and serotonin hyperfunction in the latter, it would seem NMS and SS are two different syndromes. However, when one reviews the mechanism of action of each, a convergence of effects seems to occur.

For instance, atypical antipsychotics were marketed initially as serotonin/dopamine ($5\text{-}HT_{2A}/D_2$) antagonists. Why was the blockade of $5\text{-}HT_{2A}$ so important that these drugs were heralded as second generation antipsychotics? The answer to that question is that by blocking serotonin $5\text{-}HT_{2A}$, these atypical antipsychotics are able to increase dopamine release in certain areas of the brain. It had been discovered that $5\text{-}HT_{2A}$ receptors lay on the axonal terminal of dopaminergic neurons and that their stimulation by serotonin caused a decline in dopamine release. However, the antagonizing effect of these new antipsychotics prevented serotonin from diminishing the release of dopamine. This atypical mechanism enabled the circumvention of bedeviling side effects such as elevated prolactin, extrapyramidal side effects (EPSEs), and cognitive decline. Additionally, serotonin-enhancing agents such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other serotonin boosting drugs are known to cause EPSEs on occasion. The most likely chemical culprit for these extrapyramidal events is the stimulation of those same $5\text{-}HT_{2A}$ receptors by increased intrasynaptic serotonin availability. The consequence of excessive serotonin stimulation of $5\text{-}HT_{2A}$ on these dopaminergic neurons is a diminution of dopamine release from dopamine neurons. It may be then that symptoms associated with both NMS and SS are the effects of a final common pathway shared by both syndromes.

Background

NMS and SS are uncommon but potentially fatal reactions associated with the use of psychotropics in the treatment of psychiatric disorders. NMS is known to be caused primarily by dopamine receptor antagonists such as antipsychotics. However, NMS has also been associated with the use of a few antinausea agents, other drugs that affect central dopaminergic neurotransmission, and even by the sudden discontinuation of antiparkinsonian medications (Strawn, Keck, & Caroff, 2007). Although NMS is considered a hypodopaminergic state, it does not necessarily develop as a result of high doses of antipsychotics. Even at low doses, antipsychotics may induce NMS in patients experiencing dehydration, exhaustion, or psychomotor exertion.

While the term "neuroleptic malignant syndrome" is widely accepted as accurate and descriptive, the same is not true for "serotonin syndrome." Some see this set of adverse effects as more than a "syndrome" and find that the terms serotonin toxicity or serotonin toxidrome more accurately convey the pathophysiology that develops (Kalueff, LaPorte, & Murphy, 2008). Those interesting diagnostic arguments aside, the term "serotonin syndrome" (SS) will be used in this article in order to address what the authors find to be a more interesting concept: are NMS and SS the same syndrome?

SS is the result of excess stimulation of central and peripheral nervous system postsynaptic serotonergic receptors by serotonin boosting agents, most often, the antidepressants. It is known to primarily occur when serotonergic agents increase serotonin neurotransmission through inhibition of

serotonin reuptake (SSRIs, TCAs, SNRIs), stimulation of serotonin release (cocaine, amphetamine, Ecstasy), increased serotonin synthesis (L-tryptophan), direct agonism of serotonin receptors (lysergic acid diethylamide [LSD], buspirone), or by inhibition of serotonin breakdown (MAOIs). The development of SS is most often the result of overdose of serotonergic agents or complex interactions between medications with different mechanisms of action that directly or indirectly modulate the serotonin system (Boyer & Shannon, 2005; Stahl, 2008). Historically, the most common cause of SS has been the combination of an MAOI with an SSRI; however, more recent reports show an increased involvement of SNRIs, TCAs, and a few analgesics (Gillman, 2006).

The development of NMS and SS differ, with SS related to increased levels of serotonin concentration, while NMS appears to be more of an idiosyncratic reaction (Odagaki, 2009). Even though 50 years has elapsed since NMS and serotonin toxicity (and not SS per se) were first reported, much remains to be learned about the pathophysiology of these potentially fatal disorders (Gillman, 2006; Nisijima et al., 2007). The purpose of this report is to describe how NMS and SS potentially intersect in their expression and pathophysiology.

Similar Expression

A comparison of the diagnostic criteria for these two syndromes reveals that their clinical symptoms have striking similarities with only minor differences (see Table 1). Characteristics that NMS and SS have in common include acute onset, hyperthermia, profound mental changes, heightened motor activity, and autonomic symptoms (Dvir & Smallwood, 2008; Fink, 1996). High fevers up to 106°F have been reported for both conditions. Agitation, confusion, and mental excitement also develop in both. Autonomic symptoms such as labile blood pressure, diaphoresis, and tachycardia occur in both SS and NMS (American Psychiatric Association, 2000; Nisijima et al., 2007). Catatonia or pyramidal rigidity is a motor symptom that is frequently associated with both SS and NMS in severe cases (Gillman, 2006). Creatine phosphokinase elevation and leukocytosis are blood abnormalities sometimes reported in both syndromes, although most frequently in NMS. The increase in CPK is an extreme symptom caused by muscle rigidity and subsequent rhabdomyolysis (Keltner & Folks, 2005). In sum, there are many overlapping aspects in the clinical presentation of SS and NMS.

Table 1. Similar Expression of Signs and Symptoms

Neuroleptic malignant syndrome	Serotonin syndrome
Hyperthermia	Hyperthermia
Altered consciousness	Altered consciousness
Motor symptoms	Motor symptoms
Autonomic instability	Autonomic instability

Similar Pathophysiology

Several hypotheses have been offered to explain the pathophysiologic similarities between NMS and SS (see Table 2). The most compelling hypothesis links NMS to dopamine hypoactivity. All antipsychotic medications share the mechanism of action of D_2 dopamine receptor antagonism. Blockage of the nigrostriatal (muscular rigidity) and hypothalamic (autonomic instability, altered thermoregulation) dopamine pathways are believed to result in the major symptoms associated with NMS (Bhanushali & Tuite, 2004). This neurochemical alteration may have a direct effect on peripheral skeletal muscles as well (Agar, 2010). However, the extreme clinical symptoms associated with NMS may not be totally explained by a simple decrease in central dopamine function. Additional neurochemical activity appears to contribute to the downstream effects associated with NMS symptomology. To illuminate the pathophysiology of NMS, Nisijima et al. (2007) studied monoamine metabolites in the cerebrospinal fluid (CSF) of NMS patients. The researchers measured the CSF levels of the following: homovanillic acid (HVA), a major metabolite of dopamine; 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin; and norepinephrine (NE), itself a metabolite of dopamine. The findings supported the dopamine-hypofunction hypothesis of NMS as the HVA levels in the active phase of NMS were significantly lower than in the control group. No significant differences in the 5-HIAA levels were found between the NMS patients and controls. Most interesting, the NE levels were significantly higher in the NMS patients than in the control group. These results demonstrated a potential role of noradrenergic hyperactivity during NMS. This evidence suggests that other monoamines are involved in the pathophysiology of NMS other than dopamine.

Table 2. Similar Expression of Cerebrospinal Fluid Measurements

Neuroleptic malignant syndrome	Serotonin syndrome
HVA↓	HVA↓
NE↑	NE↑
5-HIAA≠[a]	5-HIAA↓[a]
GABA↓	GABA↓

[a]The difference might be explained by the fact that when serotonin syndrome is caused by reuptake inhibiting antidepressants, less serotonin is being metabolized to 5-HIAA because that metabolism occurs in the neuron, not in the synapse.

HVA, homovanillic acid, a dopamine metabolite; NE, norepinephrine; 5-HIAA, 5-hydroxyindoleacetic acid, a serotonin metabolite; GABA, gamma aminobutyric acid.

SS is a drug-induced manifestation of elevated serotonin, which depends on the potency and admixture of the serotonergic medications precipitating the clinical manifestations (Gillman, 2006). Several subtypes of serotonin (i.e., 5-HT_{1A}, 5-HT_{2A}, 5-HT_{3A}) have been implicated in the development of SS, but as the clarifying lens of numerous reports has grown, it appears it is 5-HT_{2A} that best accounts for the pathophysiogical changes often seen (Glennon, 1990; Nisijima, Yoshino, Yui, & Katoh, 2001). For example, hyperstimulation of the 5-HT_{2A} receptor in the hypothalamus has been postulated to cause thermodysregulation, resulting in hyperthermia (Mazzola-Pomietto, Aulakh, Wozniak, Hill, & Murphy, 1995; Stahl, 2008). Hyperthermia is also related to muscle overactivity (Dvir & Smallwood, 2008). Both 5-HT_{2A} modulation of hypothalamic thermoregulatory mechanisms and down-regulation of dopaminergic striatal neurons offer explanations in concert with the central question of this article.

Increased serotonin activity in the brain also affects the NE, dopamine, and glutamate systems. Shioda, Nisijima, Yoshino, and Kato (2004) reported an increase in serotonin, dopamine, NE, and glutamate in the hypothalamus of rats treated with an SSRI and an MAO inhibitor. The autonomic symptoms associated with SS such as diaphoresis and tachycardia point to a hyperactive noradrenergic system. Thus, monoamines other than serotonin are implicated in the abnormalities associated with SS just as they are in NMS. An evaluation of NMS and SS reveals that multiple monoamines are responsible for the abnormalities accounting for both syndromes. Based on the findings as mentioned earlier, Nisijima et al. (2007) hypothesized that the pathophysiology of the two syndromes may intersect and share a final common pathway.

Minimizing the Impact of NMS and SS

Because of the common expression and pathophysiology of NMS and SS, differentiating between the two syndromes is difficult. Diagnosis of NMS and SS remains one of exclusion with no diagnostic tests or features pathognomonic for these syndromes. Treatment of NMS and SS requires expert judgment after weighing the alternatives and considering the range of manifest symptoms (Graudins, Stearman, & Chan, 1998; Sachdev, 2005). Aggressive and timely intervention is vital because of the potential for fatal outcomes. The similarities between NMS and SS speak to the legitimacy of utilizing common treatment strategies in both. Immediate withdrawal of the offending agent followed by supportive care is the treatment of choice for most cases. Supportive care includes the infusion of intravenous fluids for hydration and treatment with benzodiazepines to manage irritation (Bartlett & Muller, 2006; Dvir & Smallwood, 2008).

Sometimes, even the most up-to-date medical care cannot prevent an adverse outcome. Agar (2010) presented a case study of NMS in the emergency department in a recent edition of this journal. Her purpose was to assist in accurate assessment. We present the following case of NMS that occurred recently (summer 2010) in the emergency room of a large teaching hospital. Though the latest technology was available, the patient could not be saved.

Case Report: Sarah M

Sarah was a 52-year-old African American who was human immunodeficiency virus-positive and had a history of cocaine abuse, post-traumatic stress disorder, and depression. Sarah used mental health services liberally and often made several visits per week to her case manager at the clinic. Although "clean and sober" for the last 5 years, Sarah complained of an inability to sleep, reporting that she had not slept well for 20 years since she witnessed the murder of two friends in a drug house where she worked as a prostitute. Sarah had been prescribed many sedative hypnotics and she denied that any of them were helpful to her. She repeatedly asked the psychiatric nurse practitioner to prescribe a sedative that was "really strong." Although Sarah was taking mirtazapine 15 mg for her depression, she often took more than prescribed because of her inability to sleep (not understanding that in the case of mirtazapine, more was not better for sleep). Sometimes, she took her brother's quetiapine because of its sedating qualities. Even with quetiapine, she stated she rarely got more than 4 h of sleep.

Sarah was admitted to the hospital for severe otitis media and mastoiditis. One day later, she was discharged on antibiotics and tramadol for pain; Sarah reported that the new pain medicine helped her sleep better. Sarah was readmitted a second time within a few days in respiratory failure requiring mechanical ventilation. Her mental status was altered and she became combative. Sarah developed NMS following haloperidol administration and her temperature climbed to 106.9°F. Four vasopressor agents were required, and despite supportive care and aggressive resuscitation, her lactic acid climbed and she did not perfuse. Sarah died shortly thereafter. Cause of death was considered to be NMS.

Comments and Nursing Implications

This case illuminates the need to better understand the pathophysiology of NMS and SS in light of the common use of psychotropics in the United States. Obviously, this was a terrible human tragedy. In thinking about this situation, one can only attempt to try to figure out how things might have been different. Since haloperidol is a common cause of NMS, it perhaps warrants special attention when given in the emergency department for agitated patients. This is particularly true if other risk factors for NMS are present. Lappa et al. (2002) identified risk factors that were or may have been present in this woman, e.g., rapid initiation of an

antipsychotic (which by definition, intramuscular haloperidol would be), exhaustion (from respiratory difficulties), electrolyte imbalance (presumed), and acquired immunodeficiency syndrome dementia (a possibility). When NMS is suspected, temperature reduction (icepacks and cooling blankets), infusions of crystalloids, intubation, and hemodialysis are all mainstays of acute treatment. Pharmacologic intervention typically involves the use of bromocriptine and dantrolene. Bromocriptine, 5 mg four times per day by mouth or by nasogastric tube, acts as a dopamine agonist, enhancing dopaminergic transmission. Intravenous dantrolene, 3 to 5 mg/kg in three or four divided doses is recommended to treat skeletal muscular rigidity. In severe NMS cases refractory to medical treatment, electroconvulsive therapy has been reported to improve some of the symptoms associated with NMS (Bhanushali & Tuite, 2004; Carbone, 2000).

Providing medication for an agitated patient in the emergency room is common practice and is needed for the safety of both the patient and the staff. However, when a high-potency antipsychotic is used, the nursing staff must provide careful scrutiny of the patient, including frequent monitoring of temperature and visual assessments. While we will never be free of tragedies occurring, increased vigilance can reduce their number.

Summary

We ask the question whether NMS and SS exist on a spectrum of the same disorder, sharing the same pathophysiology. Our question is supported in the literature as others ponder the same question (Demirkiran et al., 1986; Fink, 1996; Kontaxakis, Havaki-kontaxaki, Christodoulou, Paplos, & Christodoulou, 2003). However, others strongly dispute the spectrum assertion based on differences in syndrome development (e.g., neuroleptic vs. antidepressant) and the manifestation of variable symptoms. To date, the available evidence is considered insufficient to support or refute any pathophysiological model (Gillman, n.d.), yet it is the view of these authors that considering NMS and SS to be related pathologies makes both heuristic and clinical sense.

References

Agar, L. (2010). Recognizing neuroleptic malignant syndrome in the emergency department: A case study. *Perspectives in Psychiatric Care*, *46*, 143–151. doi:10.1111/j.1744-6163.2010.00250.x

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision).Washington, DC: American Psychiatric Association.

Bartlett, D., & Muller, A. (2006). Serotonin syndrome: A subtle toxicity. *Journal of Emergency Medicine*, *32*, 277–279.

Bhanushali, M., & Tuite, P. (2004). The evaluation and management of patients with neuroleptic malignant syndrome. *Neurologic Clinics of North America*, *22*, 389–411.

Boyer, E., & Shannon, M. (2005). The serotonin syndrome. *New England Journal of Medicine*, *352*, 1112–1120.

Carbone, J. (2000). The neuroleptic malignant and serotonin syndromes. *Psychiatric Emergencies*, *18*(2), 317–325.

Demirkiran, M., Jankovic, J., & Dean, J. (1986). Ecstasy intoxication: An overlap between serotonin syndrome and neuroleptic malignant syndrome. *Clinical Neuropharmacology*, *19*, 157–164.

Dvir, Y., & Smallwood, P. (2008). Serotonin syndrome: A complex but easily avoidable condition. *General Hospital Psychiatry*, *30*, 284–287. doi:10.1016/j.genhosppsych.2007.09.007

Fink, M. (1996). Toxic serotonin syndrome or neuroleptic malignant syndrome? *Pharmacopsychiatry*, *29*, 159–161.

Gillman, P. K. (n.d.). *Neuroleptic malignant syndrome and serotonin toxicity*. Retrieved from http://www.psychotropical.com/4_st_nms.shtml

Gillman, P. K. (2006). A review of serotonin toxicity data: Implications for the mechanism of antidepressant drug action. *Biological Psychiatry*, *59*, 1046–1051. doi:10.1016/j.biopsych.2005.11.016

Glennon, R. A. (1990). Serotonin receptors: Clinical implications. *Neuroscience & Behavioral Reviews*, *14*, 35–47. doi:10.1016/S0149-7634(05)80158-7

Graudins, A., Stearman, A., & Chan, B. (1998). Treatment of the serotonin syndrome with cyproheptadine. *Journal of Emergency Medicine*, *16*, 615–619. doi:10.1016/S0736-4679(98)00057-2

Kalueff, A. V., LaPorte, J. L., & Murphy, D. L. (2008). Perspectives on genetic animal models of serotonin toxicity. *Neurochemistry International*, *52*, 649–658.

Keltner, N., & Folks, D. (2005). *Psychotropic drugs* (4th ed.). St. Louis, MO: Elsevier.

Kontaxakis, V. P., Havaki-kontaxaki, B. J., Christodoulou, N. G., Paplos, K. G., & Christodoulou, G. N. (2003). Olanzapine-associated neuroleptic malignant syndrome: Is there an overlap with the serotonin syndrome? *Annals of General Hospital Psychiatry*, *2*, 10. doi:10.1186/1475-2832-2-10. Retrieved from http://www.general-hospital-psychiatry.com/content/2/1/10

Lappa, A., Podesta, M., Capelli, O., Castagna, A., Di Placido, G., Alampi, D., & Semeraro, F. (2002). Successful treatment of a complicated case of neuroleptic malignant syndrome. *Intensive Care Medicine*, *28*, 976–977. doi:10.1007/s00134-002-1241-6

Mazzola-Pomietto, P., Aulakh, C. S., Wozniak, K. M., Hill, J. L., & Murphy, D. L. (1995). Evidence that 1-(2,5-dimethyoxy-4-iodophenyl)-2-aminopropane (DOI)-induced hyperthermia in rats is mediated by stimulation of 5-HT2A receptors. *Psychopharmacology*, *117*, 193–199. doi:10.1007/BF02245187

Nisijima, K., Shioda, K., & Iwamura, T. (2007). Neuroleptic malignant syndrome and serotonin syndrome. In H. Sharma

(Ed.), *Neurobiology of Hyperthermia* (pp. 81–104). Amsterdam: Elsevier.

Nisijima, K., Yoshino, T., Yui, K., & Katoh, S. (2001). Potent serotonin (5-HT)$_{2A}$ receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. *Brain Research*, *890*, 23–31.

Odagaki, Y. (2009). Atypical neuroleptic malignant syndrome or serotonin toxicity associated with atypical antipsychotics? *Current Drug Safety*, *4*(1), 84–93.

Sachdev, P. S. (2005). A rating scale for neuroleptic malignant syndrome. *Psychiatry Research*, *135*, 249–256. doi:10.1016/j.psychres.2005.05.003

Shioda, K., Nisijima, K., Yoshino, T., & Kato, S. (2004). Extracellular serotonin, dopamine and glutamate levels are elevated in the hypothalamus in a serotonin syndrome animal model induced by tranylcypromine and fluoxetine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *28*, 633–640.

Stahl, S. (2008). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (3rd ed.). New York: Cambridge University Press.

Strawn, J. R., Keck, P. E. Jr, & Caroff, S. N. (2007). Neuroleptic malignant syndrome. *American Journal of Psychiatry*, *164*(6), 870–876. doi:10.1176/appi.ajp.164.6.870